Complete Summary

GUIDELINE TITLE

Adjuvant therapy for stage II colon cancer following complete resection.

BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Disease Site Group. Figueredo A, Germond C, Maroun J, Browman G, Walker-Dilks C, Wong S. Adjuvant therapy for stage II colon cancer following complete resection [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2000 Dec [online update]. 30 p. (Practice guideline report; no. 2-1). [70 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Colon cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Gastroenterology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make recommendations regarding the use of adjuvant therapy in the treatment of resected stage II colon cancer

TARGET POPULATION

Adult patients with stage II colon cancer following complete resection

INTERVENTIONS AND PRACTICES CONSIDERED

Adjuvant therapy for stage II colon cancer following complete resection, including the following regimens:

1. Adjuvant chemo- and/or immunotherapy with Bacillus Calmette-Guerin (BCG)
    - Semustine and 5-fluorouracil (5-FU)
    - Semustine and 5-fluorouracil with Bacillus Calmette-Guerin
    - Bacillus Calmette-Guerin
    - Semustine, vincristine, and 5-fluorouracil
    - Mitomycin C and 5-fluorouracil
2. Systemic therapy with 5-fluorouracil and levamisole
3. Systemic therapy with 5-fluorouracil modulated by leucovorin (folinic acid)
4. Chemotherapy administered by portal vein infusion (PVI)
    - 5- fluorouracil and heparin
    - Heparin
    - Mitomycin C plus 5- fluorouracil and heparin
    - Urokinase
    - Fluorodeoxyuridine (FUDR)
5. Other trials
    - Chemotherapy delivered by the intraperitoneal route
    - Passive immunotherapy with Bacillus Calmette-Guerin, with or without chemotherapy
    - Preoperative immunostimulation
    - Active specific immunotherapy with autologous tumour cells and Bacillus Calmette-Guerin

MAJOR OUTCOMES CONSIDERED

- Overall survival is the primary outcome of interest.
- Disease-free survival and treatment toxicity are secondary outcomes.

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Original Guideline: August 1997

MEDLINE was searched (1966 to March 1997) using the terms "colonic neoplasms", "adjuvant chemotherapy", "immunologic adjuvant"," radiotherapy", "Duke(s)" and the methodological terms: "clinical trial", "review", "meta-analysis", "double-blind method", "random allocation", and "guideline". Personal reprint files were searched, and the relevant studies from bibliographies were reviewed.

December 2000 Update

The original literature search has been updated using MEDLINE (through December 2000), CANCERLIT (through November 2000), the Cochrane Library (Issue 4, 2000), and the conference proceedings of the 1998 to 2000 annual meetings of the American Society of Clinical Oncology (ASCO) and the American Society for Therapeutic Radiology and Oncology.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. They were randomized controlled trials (RCTs) with appropriate comparison groups or meta-analyses of RCTs involving patients with stage II colon cancer who had undergone surgery with curative intent and were randomized to receive adjuvant therapy.
2. The main outcome of interest was survival. Disease-free survival and treatment toxicity were also considered.
3. This review considered clinical trials published after 1987. Buyse et al summarized results of randomized trials of adjuvant therapy for colorectal cancer up to that year. Results of this meta-analysis are discussed in the section titled "Interpretative Summary" in the original guideline document.

NUMBER OF SOURCE DOCUMENTS

Original Guideline: August 1997

Three meta-analyses, 31 randomized controlled trials (RCTs), and one evidence-based consensus report were reviewed.

2000 Update

Four published meta-analyses and new or updated reports of 19 randomized trials were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Original Guideline: August 1997

Individual patient data were not available for review. For some trials the actual number of patients and events in stage II patients was reported (actual data). If not reported, the number of patients and deaths as well as survival and disease-free survival are estimated from published tables or graphs (estimated data). For pooled analysis these data did not allow statistical adjustments for covariates. Data on survival were combined at the time of follow-up reported in each study, but it should be noted that the length of follow-up differs across studies. Combining data in this way assumes a constant hazard ratio of risks between the groups being compared. Data across studies were combined using meta-analysis software, Metaanalyst[0.988] (Dr. Joseph Lau, Boston, MA). Results are expressed as the odds ratios (OR) with 95% confidence intervals (CI), where an OR <1.0 for the event of interest (e.g., death) favours the experimental treatment and an OR >1.0 favours the control. The OR expresses the odds of an event in the treatment group relative to the odds of the event in the control group. Data were analyzed by both fixed effects (Mantel-Haenszel) and random effects models. For calculation of the OR and the 95% CI for survival data the denominator used was the number of patients randomized rather than those at risk at the time of follow-up, which will overestimate the precision of the confidence limits. These narrower limits do not alter the conclusions in this case.

December 2000 Update

New evidence that has emerged since the completion of the original guideline was not added to the meta-analysis.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Original Guideline: August 1997

Members of the Gastrointestinal Cancer Disease Site Group (DSG) agreed that, based on the current evidence, it was reasonable and appropriate at this time to discourage the use of adjuvant treatment for patients with stage II colon cancer, with the understanding that patients with "high-risk" disease understand their prognosis and the limited benefits shown for adjuvant treatment to date. Patients

with stage II disease should be encouraged to participate in randomized controlled trials of adjuvant therapy. Therapeutic trials have not clearly demonstrated an improvement in survival or a consistent improvement in delaying tumour relapse. Longer follow-up, a greater number of patients, and an enlarged meta-analysis of these trials with subgroup stratification may well provide more precise data. In the meantime, patients with stage II disease and poorer prognosis, specifically those with aneuploidy, tumour perforation, adherence, or invasion of neighbouring structures, or bowel obstruction, should be made aware of their prognosis, and the uncertain role of adjuvant therapy. These patients should be encouraged to participate in clinical trials of adjuvant therapy. Further investigation of prognostic factors in stage II colon cancer should continue, including those already listed above, and others such as allelic loss of chromosome 18q, p53 and thymidylate synthase elevation, and the presence of micrometastases in regional lymph nodes discovered by cytokeratin immunostaining.

December 2000 Update

A summary of the new evidence that emerged since the completion of the original guideline report was reviewed by the Gastrointestinal Cancer DSG members. The DSG members agreed that the new evidence is consistent with the data used to inform the initial practice guideline and that the recommendations of the original report should remain unchanged.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Original Guideline: August 1997

Practitioner feedback was obtained through a mailed survey of 92 practitioners in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Those not responding received a follow-up reminder at two weeks, four weeks (mail), and 12 weeks (telephone). The results of the survey were reviewed by the Gastrointestinal Cancer Disease Site Group (DSG).

This practice guideline reflects the integration of the draft recommendations in the External Review process and has been approved by the Gastrointestinal Cancer Disease Site Groups and the Practice Guideline Coordinating Committee.

This practice guideline was also reviewed by two external reviewers prior to publication in the journal Cancer Prevention and Control.

December 2000 Update

The new information from review and updating activities was not subject to external review because the new evidence is consistent with the data used to inform the original guideline.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Adjuvant therapy is not recommended at this time for routine management of patients with resected stage II colon carcinoma.
- Patients with stage II disease and "high-risk" factors (bowel obstruction, tumour adhesion, invasion, perforation, or aneuploidy) have a poorer prognosis, similar to stage III patients. For individual management, these patients should be made aware of their prognosis. Treatment can be considered after explaining the uncertainty of the value of the therapy to the patient.
- The enrollment of resected stage II "high-risk" patients in clinical trials is encouraged. Trials comparing adjuvant therapy with observation are needed and are ethically acceptable in stage II colon cancer.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Original Guideline: August 1997

There are three published meta-analyses and 31 randomized controlled trials (RCTs) available for review. Results from the 11 of 31 randomized controlled trials that provided adequate data were pooled.

December 2000 Update

The recommendations are supported by meta-analyses and randomized trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Original Guideline: August 1997

The 31 randomized controlled trials (RCTs) are grouped according to the type of therapy and whether the control groups received observation or other treatment. Because trials usually included patients with both stage II and stage III disease, both complete trial results and a stage II subset analysis were considered. Although overall trial results showed a survival benefit for adjuvant treatments, the benefit was not significant for stage II patients. A meta-analysis of data for stage II patients available from 11 trials indicated no significant reduction in the odds of death for adjuvant treatment compared with observation (odds ratio [OR], 0.83; 95% confidence intervals [CI] 0.62 to 1.10). The odds ratio for patients receiving chemotherapy by portal vein infusion (PVI) was 0.62 (95% CI 0.35 to 1.11).

December 2000 Update

The new evidence identified by the updated literature search is consistent with the data used to inform the original practice guideline.

POTENTIAL HARMS

Original Guideline: August 1997

Toxicity of 5-fluorouracil (5-FU) combined with either levamisole and leucovorin was mild to moderate, consisting mostly of stomatitis, diarrhea, and myelosuppression, and requiring hospitalization in 5% of patients. 5-fluorouracil plus levamisole was associated with transient neurotoxicity in 18% of patients. Toxicity related to portal vein infusion was mild, rare, and mostly related to leukopenia and diarrhea; 1% of patients experienced bowel perforation.

December 2000 Update

The new evidence identified by the updated literature search is consistent with the data used to inform the original practice guideline.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Results of adjuvant treatment for stage II colon cancer derive mainly from clinical trials which also include patients with stage III, and occasionally stage I colon cancer, as well as patients with rectal cancer. Therefore, results for stage II colon cancer are based upon subgroup analysis and thus, the generalizability of results is open to some interpretation. These circumstances require consideration of the overall trial results and subgroup analysis of patients with stage II colon cancer.

- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Disease Site Group. Figueredo A, Germond C, Maroun J, Browman G, Walker-Dilks C, Wong S. Adjuvant therapy for stage II colon cancer following complete resection [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2000 Dec [online update]. 30 p. (Practice guideline report; no. 2-1). [70 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1997 Aug 25 (updated online 2000 Dec)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Gastrointestinal Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Gastrointestinal Cancer Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Adjuvant therapy for stage II colon cancer following complete resection. Summary. Toronto (ON): Cancer Care Ontario, 1997 Aug 25 (updated online 2000 Dec). Electronic copies: Available from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995 Feb;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 5, 1999. The information was verified by the guideline developer as of February 22, 1999. This NGC summary was updated by ECRI on December 3, 2001. The updated information was reviewed by the guideline developer as of January 10, 2002. This summary was updated again by ECRI on May 14, 2004. The information was verified by the guideline developer on June 2, 2004.

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